PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000090	07.01.2005	07.01.2004

International Patent Classification (IPC) or both national classification and IPC
G06F19/00, G01N33/68

Applicant
BIOVISION AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000090

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2-6,8

because:

☒ the said international application, or the said claims Nos. 22 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2-6,8

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,7(partially),9-24(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1,7,9-24
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1,7,9-24
Industrial applicability (IA)	Yes:	Claims	1,7,9-21,23,24
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item III.

Claim 22 relates to subject-matter considered by this authority to be covered by the provisions of R. 67.1(v) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art. 34(4)(a)(i) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

Invention 1: claims 1, 7 (partially), 9-24 (partially)
A method of providing a representative, non-redundant overview of the peptide content of a sample type by analyzing a plurality of samples using its peptide topology, wherein the method comprises the steps a)-b) as listed in claim 1.

Invention 2: claims 2,3, 7 (partially), 8-24 (partially)
A method of predicting the sequence of proteins comprising the steps a)-e) of claim 2.

Invention 3: claims 4-6,7 (partially), 8,9-24(partially)
A method for identifying peptides suitable to be used as marker panels or surrogate for a known peptide as defined by claims 4-6, wherein the last step c) or d) comprises: (i) selecting pairs of potential peptides, which exhibit a difference in the degree of correlation between the experimental groups, or (ii) no correlation of their respective signal intensities, or (iii) which exhibit a degree of correlation with a known peptide above a certain threshold.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present application does not meet the requirements of R.13.1 and 13.2 PCT, because the subject-matter of independent claims 1-6 do not involve the same corresponding "special technical features" according to R. 13.2 PCT, nor are they linked by a single general inventive concept according to R.13.1 PCT.

The methods of claims 1-6 share the following common technical features:
step (i) providing a respective mass spectrum for each sample of said plurality of samples, wherein signal intensity peaks correspond to potential peptides,
step (ii) computing the measures of correlation between the signal intensities of said potential peptides.

The steps c) and d) of claim 1 are not included in the other independent claims 2-6. Accordingly, the features b), d) and e) of claim 2 have no counterparts in claims 1, 3-6 and so on.

The problem underlying the single general concept can therefore be considered as the provision of a method for providing an overview of the peptide content of a sample or predicting the sequence of a peptide or identifying peptides suitable as marker panels or surrogate. The solution forming the single general concept is a computational method based on mass spectrometric signals comprising the above listed common "special technical features" (i) and (ii).

However, the documents D1 and D2 disclose such methods with technical features (i) and (ii). D1 discloses a method for identifying microorganisms by comparing mass spectrometric data of a microorganism with reference spectra from a database. D1 further discloses that the empirical signals (Sem, see paragraph [0021] in D1) are obtained by a comparison of a multiplicity of mass spectra of different samples of the same microorganism. A correlation between the signal intensities of said samples is calculated (see col. 6, lines 10-24). It is also clear that the signals derive from peptides of said samples (see paragraph [0019]).
Thus, the single general concept as defined above is anticipated by D1.
D2 also anticipates the single general concept for the following reasons:
D2 discloses a method in which the mass spectrum for a sample is acquired in triplicate, wherein signal intensity peaks correspond to potential peptides (see table 3, definition of biomarkers). Thereafter, a measure of correlation is computed between the signal intensities of said potential peptides by principal component analysis and hierarchical cluster analysis, which are both well recognised methods of correlation of data (see p. 120, right column, first two paragraphs).
In light of the documents D1 and D2, the above mentioned single general concept is

neither novel nor inventive and can thus not be regarded as the single general inventive concept as required by R.13.1 and 13.2 PCT.

Re Item V.

1.1 Reference is made to the following documents:

D1: DE 100 38 694 A (ANAGNOSTEC GES FUER ANALYTISCH) 14 February 2002 (2002-02-14)

D2: VAIDYANATHAN SEETHARAMAN ET AL: "Flow-injection electrospray ionization mass spectrometry of crude cell extracts for high-throughput bacterial identification." JOURNAL OF THE AMERICAN SOCIETY FOR MASS SPECTROMETRY. UNITED STATES FEB 2002, vol. 13, no. 2, February 2002 (2002-02), pages 118-128, XP002273858 ISSN: 1044-0305

D3: PEVZNER PAVEL A ET AL: "Efficiency of database search for identification of mutated and modified proteins via mass spectrometry" GENOME RESEARCH, vol. 11, no. 2, February 2001 (2001-02), pages 290-299, XP002273859 ISSN: 1088-9051

D4: WILKES JON G ET AL: "Defining and using microbial spectral databases." JOURNAL OF THE AMERICAN SOCIETY FOR MASS SPECTROMETRY. UNITED STATES JUL 2002, vol. 13, no. 7, July 2002 (2002-07), pages 875-887, XP002273860 ISSN: 1044-0305

D5: WO 2004/008371 A (APPEL RON ;HERNANDEZ PATRICIA (CH); INST SUISSE DE BIOINFORMATIQUE) 22 January 2004 (2004-01-22)

1.1 The term "correlation associated networks" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

2. Novelty (Art. 33(2) and 33(3) PCT)

The following remarks relate to invention 1.

The above given lack of clarity notwithstanding, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

2.1 D1 discloses a method for identifying microorganisms by comparing mass spectrometric data of a microorganism with reference spectra from a database. D1 further discloses that the empirical signals (Sem, see paragraph [0021] in D1) are obtained by a comparison of a multiplicity of mass spectra of different samples of the same microorganism. A correlation between the signal intensities of said samples is calculated (see col. 6, lines 10-24). It is also clear that the signals derive from peptides of said samples (see paragraph [0019]). The method of D1 does, however, not comprise steps c and d listed in claim 1 of the present application.

2.2 D2 discloses a method in which the mass spectrum for a sample is acquired in triplicate, wherein signal intensity peaks correspond to potential peptides (see table 3, definition of biomarkers). Thereafter, a measure of correlation is computed between the signal intensities of said potential peptides by principal component analysis and hierarchical cluster analysis, which are both well recognised methods for the correlation of data (see p. 120, right column, first two paragraphs). Steps c) and d) of claim 1 are lacking in D2.

2.3 D3 doscloses an algorithm for cross-correlating and clustering related spectra in large collections of uncharacterized spectra. D3 anticipates the subject-matter of claim 1 for the following reasons:
(a) Mass spectra for a plurality of samples, wherein signal intensitiy peaks correspond to potential peptides, are provided.
(b) The measures of correlation between the signal intensities of said potential peptides are computed (see pages 292-294 of D3).
(c) Potential peptides are grouped together, which exhibit a degree of correlation among each other above a certain threshold (see p. 294, chapter on spectral alignment and fig. 3 and 4).
(d) Assigning one representative potential peptide is shown in table 1.

2.4 D4 discloses general protocols for rapid identification of unknown bacterial samples. On p. 885, a protocol is disclosed which anticipates the subject-matter of claim for the following reasons:

Steps 1 and 2 on p. 885, left column, anticipate the subject-matter of claim 1.a).

Step 3 anticipates the subject-matter of claim 1.b and c, since it is stated that the spectra are compared to each other using one or more 2-D CV score plots which is a way of computing the measures of correlation between signal intensities. From fig. 8 and its discussion on p. 883, it is also clear that the peptides exhibiting a degree of correlation are grouped together.

Step 4 anticipates the subject-matter of claim 4, since one representative (a neighbor "known") is assigned.

2.5 Dependent claims 7, 9-24 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).